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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/596,479	03/29/2007	Bradley L. Urquhart	10935-35	7049

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
02/01/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,479	URQUHART ET AL.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,7-15 and 19-23* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,7-14 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. Applicants' arguments, filed 10/8/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Applicant's arguments, see p. 7, filed 10/8/2009, with respect to the rejection under 35 USC 112, 2nd paragraph have been fully considered and are persuasive. The rejection of claim 1 has been withdrawn.

The claim amendment removing "removal of mesna" and "derivatives" language from the claims removes the basis for this rejection.

3. Applicant's arguments, see p. 7, filed 10/8/2009, with respect to the rejection under 35 USC 112, 1st paragraph have been fully considered and are persuasive. The rejection of claims 1, 3-5 and 7-14 has been withdrawn.

The removal of "derivatives" of mesna from the claims removes the rejection basis.

4. Applicant's arguments with respect to the rejection under 35 USC 103 have been fully considered but they are not persuasive:

Claims 1, 3-5, 7-14 and 19-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pendyala, et al. ("Intravenous Ifosfamide/Mesna Is Associated with Depletion of Plasma Thiols without Depletion of Leukocyte Glutathione"; 2000; Clinical

Cancer Research; 6(4): 1314-1321; cited in a previous Office Action); and Cohen ("Methyl group deficiency and guanidine production in Uremia; 2003 Feb; Molecular and Cellular Biochemistry; 244(1-2): 31-36; cited in a previous Office Action); in view of Wilcox (WO 01/30352 A1; 2001; IDS 8/3/2006 reference).

With respect to claims 1, 3-5 and 7-14 the rejection is maintained for the reasons of record. The addition of claims 19-23 to the rejection is necessitated by the claim amendment adding these new claims.

The rejection of record is applicable to new claim 19 for the reasons of record, since the rejection basis is administration of mesna to a subject with ESRD, where dialysis is performed on the subject, which would have been obvious as outlined on the record.

With respect to the amounts recited in new claims 20-23, Pendyala teaches a linear reduction of total cysteine with respect to the total mesna concentration in the plasma, ranging from 0 to 50 µg/mL, where levels of total cysteine approach 0 at 50 µg/mL; mesna, when dosed at amounts to give blood concentrations of 5, 25 or 50 ug/ml resulted in increasing percentages of cysteine and homocysteine recovery, up to about 30-40% (p. 1320, Figure 8). Assuming a blood volume of 5 L, a mesna dose of 250 mg would be expected to give a maximum concentration of 50 µg/mL; 250 mg dosed to a 70 kg individual corresponds to 3.57 mg/kg dose. Pendyala does not specifically teach the dosing amounts and frequencies of claims 20-23.

It would have been obvious to one of ordinary skill in the art at the time of the invention to dose mesna in amounts including 3.57 mg/kg/dose, before thrice weekly

dialysis sessions, giving an amount of claim 23 and weekly amounts of 10.7 mg/kg, within the ranges of claims 20-22. It would also have been obvious to optimize the amount dosed, for optimal efficacy while minimizing side effects of mesna in an individual with ESRD, starting with the target amount of 3.57 mg/kg/dose; such optimization would also have been expected to give amounts within each of claims 19-23.

Applicant argues that the deliberate extrapolation of the results reported in Ventura and in Friedman is not proper, arguing that the ignoring of potential saturation behaviour approach was admitted in a prior Office Action; that this is completely wrong to assume relationships between dose and t-Hcy levels are linear. This is not persuasive; assuming linear behavior is an approximation that is practiced in the art when partial data is present; indeed, this approach is validated by the data of Pendyala (p. 1319, Figure 7, which demonstrates a linear reduction in total cysteine as a function of total mesna concentration in the plasma. Certainly, saturation behaviour is expected as a drug is dosed in higher amounts; however, linear behavior is a model that normally describes behaviour at lower amounts. The calculation that was previously presented is based on data available, and gives an expectation that the result disclosed in the instant specification is not somehow unexpected over what is known in the art.

Applicant argues that Pendyala's teaching that mesna is administered intravenously to patients with functioning kidneys at a dose rate ranging from 2 g/m^2/day to 8 g/m^2/day, which corresponds to 3.46 g/day to 13.84 g/day, or 5.29-20.76 g over the 36 hour protocol, is significantly greater (94 to 98% greater mesna) than the data of

Figure 2, or about 350 mg dosed per patient; and that this difference was not taken into account in the calculation. Perhaps it would be better to take additional corrections into account in performing the calculation. However, it is assumed that applicant is most knowledgeable about more accurate values which should be applied in a calculation of this type. It is noted that the data disclosed are not commensurate in scope with any of the instant claims for at least the following reasons: 1) the only amount dosed is 5 mg/kg mesna; none of the claims are limited to this amount; 2) the claims under examination all use open language construction, "comprising" which permits additional agents that would reduce tHcy; in contrast, the data disclosed are limited to administering only mesna. The rejection may be maintained for embodiments outside of the limited scope for which data are disclosed, even if the calculation presented is somehow inaccurate as a qualitative/semiquantitative prediction model.

Applicant further argues that it is improper to assume the relationship between dose and activity is linear; that administration of 350 mg dose would not have been expected to give a 29% reduction in plasma t-Hcy. Considering the fact that 50 ug/mL total plasma mesna results in near 0 levels of total cysteine plasma levels, and that 50 ug/mL can be achieved by approximately 3.57 mg/kg dose (see above), based on Figure 7 of Pendyala, a substantial reduction of tHcy would be expected for even a 5 mg/kg dose when coupled with dialysis. As is also discussed above, even if the calculation does not use the best approximations, the data disclosed in the specification are not commensurate in scope with any of the instant claims for the reasons discussed above.

Applicant further argues the calculations and reasoning reported in the Office Action were flawed is the assumption that NAC is a "derivative" of mesna. The point is that both compounds have sulfhydryl groups; this part of the molecule would be responsible for reduction of homocystine to homocysteine and exchange of homocysteine bound to albumin with the thiol containing group. This point of view is also supported by the Urquhart et al. reference, 10/8/2009 IDS reference, that indicates both NAC and mesna effectively exchanged with covalently bound Hcy, although the mesna had a greater effect than equimolar NAC (abstract); i.e., both compounds were recognized in the art to have the same exchange activity, albeit one with a greater effect than the other when used at the same concentration. It is not clear what the purpose of discussing DMSA is, since this molecule is not part of the basis for the rejection of record; the amended claims no longer encompass DMSA.

Applicant argues that the calculations and reasoning reported in the Office Action are flawed because Pendyala never administered mesna on its own, but always with ifosfamide; that Pendyala actually teaches individual effects of ifosfamide and mesna are unclear (because the two were administered together); that Pendyala merely presents in vitro data showing that mesna can reduce homocystine to homocysteine; therefore there is not direct evidence in Pendyala that mesna on its own reduced homocystine in vivo to homocysteine which is then cleared by renal excretion; that Pendyala admits that this conclusion cannot be made given the potentially confounding effect of co-administration of ifosfamide. It is noted that the instant claims do not exclude ifosfamide. However, the rejection is from the point of view that it would have

been obvious to administer mesna alone (without ifosfamide) motivated by the expected reduction of homocysteine levels in ESRD patients. Figure 7 clearly provides evidence of reduction of total cysteine concentration with increasing mesna in plasma, an *in vivo* result; a similar effect would be expected for homocysteine. On p. 1318, 3rd paragraph, it is indicated that an inverse correlation was observed between total mesna plasma concentration and total cysteine or total homocysteine plasma concentration for all of the patients, with a reference to Figure 7 for cysteine, but noted the analogous data for homocysteine is not shown. This is also an *in vivo* result. These results lead to the expectation that when mesna is administered to a subject with ESRD, accompanied by dialysis a similar reduction in homocysteine will be expected.

Applicant argues that with respect to removal of mesna by dialysis the NAC results are somehow improper to use in a discussion. NAC is indeed a similar compound to mesna, with similar activity in effective exchange of homocysteine bound to albumin, as discussed above. Additionally, the presence of free mesna in solution would lead to an expectation of some level of removal during dialysis, meeting the claim limitation. The burden has been shifted to applicant to demonstrate that this would not occur when the obvious method steps are carried out. This burden has not been met.

Applicant has made some arguments with respect to dimesna. Although it is agreed that some of the claims now encompass a method that includes the administration of dimesna, this compound is not under examination; therefore the arguments with respect to dimesna are not relevant to the instant rejection.

Applicants argue that there is no rational underpinning to the conclusion of obviousness. This is not persuasive. Such a rational underpinning has been presented on the record, and was first outlined in the Office Action of 5/12/2008.

5. Applicant's arguments, see p. 18, filed 10/8/2009, with respect to the rejection under 35 USC 102/103 have been fully considered and are persuasive. The rejection of claims 1, 3-5, 7-8 and 13-14 has been withdrawn.

The claims have been amended to exclude "derivatives" of mesna; therefore NAC (the compound taught by Friedman) no longer reads on the instant claims.

6. Applicant's arguments, see p. 16, filed 10/8/2009, with respect to the rejection of claims 9-12 under 35 USC 103 as obvious over Friedman have been fully considered and are persuasive. The rejection of claims 9-12 has been withdrawn.

The rejection is withdrawn based on the claim amendment removing "derivatives" of mesna.

Conclusion

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Examiner, Art Unit 1628

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642